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Supplemental Iodide for Preterm Infants and Developmental Outcomes at 2 Years: an RCT

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Table of contents: The iodide recommendation for preterm enteral nutrition is 30-40μg/kg/day but only 1μg/kg/day for parenteral nutrition. We investigated whether supplemental iodide improved developmental outcomes.

WHAT'S KNOWN ON THIS SUBJECT

The iodide recommendation for preterm enteral nutrition is 30-40μg/kg/day but 1μg/kg/day for parental nutrition. Iodide is needed to produce thyroid hormones, which are essential for normal brain development. Observational studies report associations between low postnatal thyroid hormones and compromised neurodevelopment.

WHAT THIS STUDY ADDS

The neutral results do not indicate that the iodide content of parenteral nutrition should routinely be increased from the current level to match the enteral level. This evidence may not apply to preterm infants on primarily parental nutrition over prolonged periods.

CONTRIBUTOR'S STATEMENT PAGE

Fiona Williams: conceptualized and designed the study, contributed to the data analysis, drafted the initial manuscript and approved the final manuscript as submitted

Robert Hume: conceptualized and designed the study, critically reviewed the manuscript and approved the final manuscript submitted

Simon Ogston, Edmund Juszczak, and Jennifer Watson: designed and contributed to the data analysis, reviewed and revised the manuscript, and approved the final manuscript submitted

Peter Brocklehurst: contributed to the study design, reviewed and revised the manuscript, and approved the final manuscript submitted

Peter Willatts and Kayleigh Stanbury: contributed to the design of the neurodevelopmental assessments, coordinated and supervised the data collection, critically reviewed the manuscript and approved the final manuscript submitted

Anita Boelen: coordinated and supervised the analysis of blood spot cards, critically reviewed the manuscript and approved the final manuscript submitted

ABSTRACT

Background The recommendation for enteral iodide intake for preterm infants is 30–40 μg/kg/day and 1μg/kg/day for parenteral intake. Preterm infants are vulnerable to iodide insufficiency and thyroid dysfunction. The hypothesis tested whether, compared to placebo, iodide supplementation of preterm infants improves neurodevelopment.

Methods A randomized controlled trial of iodide supplementation versus placebo in infants <31 weeks' gestation. Trial solutions (sodium iodide or sodium chloride; dose 30μg/kg/day) were given within 42 hours of birth to the equivalent of 34 weeks' gestation. The only exclusion criterion was maternal iodide exposure during pregnancy or delivery. Whole blood levels of thyroxine, thyrotropin and thyroid binding globulin were measured on four specific postnatal days. The primary outcome was neurodevelopmental status at two years' of age, measured using the Bayley-III scales. The primary analyses are by intention-to-treat and data are presented also for survivors.

Results 1,273 infants (637 intervention, 636 placebo) were recruited from 21 UK neonatal units. 131 infants died, and neurodevelopmental assessments were undertaken in 498 iodide and 499 placebo supplemented infants. There were no significant differences between the intervention and placebo groups in the primary outcome: mean difference Cognitive score, -0.34, 95% confidence interval (CI) -2.57 to 1.89; Motor composite score, 0.21, 95% CI -2.23 to 2.65; Language composite score, -0·05, 95%CI -2.48 to 2.39. There was evidence of weak interaction between iodide supplementation and hypothyroxinemic status in the Language composite score and one subtest score.

Conclusions Overall iodide supplementation provided no benefit to neurodevelopment measured at 2 years of age.

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249 words

INTRODUCTION

Thyroid hormone is essential for normal brain development *in-utero* and for the first two years of life. Brain damage through deficiency of thyroxine (T4) is irreversible. Congenital hypothyroidism is the most extreme form of thyroid hormone deficiency. A milder form of deficiency, transient hypothyroxinemia, is characterized by low or normal levels of thyrotropin (TSH) and low T4 levels. Transient hypothyroxinemia is common in preterm infants,[1] its etiology is multifactorial[2-6] and includes iodide deficiency.[7,8] The European guideline for preterm neonatal enteral iodide intake is 11–55μg/kg/day;[9] although, evidence from balance studies suggests that the intake for healthy preterm infants should be a minimum of 30–40μg/kg/day.[7] The guideline for parenteral nutrition is 1μg/kg/day.[10,11]

The iodide requirement of extreme preterm infants is complex and difficult to assess. Neonates have very small iodine reserves,[12] are vulnerable to iodine toxicity,[13] and their immature physiology can demand higher levels of some nutrients, especially ions, relative to the term neonate.[14] Extreme preterm infants are fed parenterally until their clinical condition improves, when the contribution of parenteral to formula/breast milk gradually decreases. Iodide balance studies of preterm infants show that they are in negative iodide balance[7,8] until their intake of nutrition is primarily enteral. Iodine is an essential component of thyroid hormones and because the preterm infant has small iodide reserves within the thyroid gland,[12] it is essential that daily nutrients provide sufficient iodide to support T4 production.

Although transient hypothyroxinemia was formerly thought of as clinically harmless, recent studies show associations with neurodevelopmental compromise.[15-20] Infants with transient hypothyroxinemia perform less well on developmental tests and this compromise persists into at least late childhood.[18] These children are predicted to perform less well at school, which has consequences for their lifetime achievements and well-being. The link between suboptimal neurodevelopment and the early iodide status of preterm infants is not well known. It is also

unknown whether iodide supplementation can confer a benefit to later outcome. Our aim was to determine whether iodine supplementation leads to improved neurodevelopmental outcome in extreme preterm infants at 2 years of age.

PATIENTS AND METHODS

I2S2 was a UK, randomized, placebo-controlled trial.[21] The trial was approved by Tayside Committee on Medical Research Ethics (08/S0501/31), Medicines and Healthcare products Regulatory Agency (CTA No. 21584/0251/001), and registered with clinical trials (NCT00638092) and EudraCT, No. 2008-001024-31. Written informed consent was obtained from the infants' parents.

Infants were eligible if they were <42 hours old, born <31 weeks' gestation in one of the trial recruiting hospitals, and had a realistic prospect of survival. The only exclusion criterion was maternal exposure to iodide during pregnancy or delivery (e.g. the use of topical iodides for skin antisepsis prior to epidural/caesarean section/other surgery, or from exposure to iodinated contrast media. Women absorbing iodide from multi-vitamins or from their habitual diet were eligible for enrollment.)

RANDOMIZATION AND MASKING

Eligible infants were randomized to intervention or placebo (with roughly equal probability) using a secure website with 24/7 telephone back-up.[21] The randomization program used a bespoke minimisation algorithm to ensure balance across hospitals on gender and gestational age (by individual week from 22-25 weeks, 26-27 weeks, and 28-30 weeks (Supplementary Table 0, Appendix). Infants from multiple births were randomized individually. Masking ensured that the research team, trial statistician, parents, neonatal staff and pharmacy were blind to the content of the trial solutions.

PROCEDURES

Mother/infants were recruited by I2S2 trained staff. Trial solutions were prescribed by medical staff following I2S2 guidance sheets. Infants received either the intervention (sodium iodide diluted to an iodide content of 75μg/ml) or placebo (sodium chloride diluted to a chloride content of 75μg/ml). The packaging and visual appearance of trial solutions were identical and the solutions could be given either parenterally or enterally. (Enteral absorption of iodide is almost complete, thus the parenteral and enteral intakes should be the same.) The dose was 30μg/kg/day, given daily from randomization until the equivalent of 34 weeks' gestational age (had the fetus remained *in-utero* referred to hereafter as equivalent gestational age).

Infant blood was collected on blood spot cards at postnatal days 7, 14, 28, and at 34 weeks' equivalent gestational age, ±1 day. Cards were sent to the Amsterdam Neonatal Screening Laboratory for estimation of T4, TSH and TBG (thyroid-binding-globulin). Detailed clinical data were collected throughout the study by trial staff.[21] Drug prescriptions, nutritional data, and level of nursing care (as an indicator of illness severity,[6] Supplementary Table 1, Appendix) were recorded on the days when trial blood samples were taken. Data were collected from study entry until 36 weeks' equivalent gestational age, including all inter-unit transfers (or from discharge home/death if these occurred before 36 weeks). Medical and social information for the period between hospital discharge and the two year follow-up was recorded on a form, completed by the person bringing the child to the appointment. Infants were assessed using the Bayley-III Scales of Infant and Toddler Development[22] at two years of age corrected for prematurity (±1 month). The Bayley-III provides information on three domains (Cognitive, Motor composite and Language composite scales, each with a population mean of 100 and standard deviation (SD) of 15) and four subtest scales (Expressive Communication, Receptive Communication, Fine Motor and Gross Motor scales, each with a mean of 10 and SD of 3). Infants were assessed using trial

personnel specifically trained to use the Bayley-III and random performances were video-recorded and audited. The setting for the interventional phase was the neonatal unit and follow-up at two years was undertaken in a hospital close to the infants' home.

There were no restrictions on medications or treatments permitted during the trial, including Levo-thyroxine if prescribed. Infants were immediately withdrawn from receiving trial solutions if they were exposed to topical iodide containing antiseptics or if iodinated contrast media was given. Such infants were monitored locally for the biochemical features of iodine toxicity on thyroid dysfunction. These infants were included in all other aspects of the trial, including the two-year follow-up.

TRIAL OUTCOMES

The primary outcome was neurodevelopmental status defined by the three domains of the Bayley-III at two years of age corrected for prematurity. Secondary outcomes were: the four subtests of the Bayley-III; Bayley-III analysed as a dichotomous outcome (death or a Bayley-III score <85 in any of the main domains versus a Bayley-III score 85+); levels of T4, TSH and TBG on postnatal days 7, 14, 28 and 34 weeks' equivalent gestational age (±1 day); various measures of neonatal type and severity of illness;[21] and prescribed drug usage.[21]

STATISTICAL ANALYSIS

To detect a difference in mean Bayley-III score of 6 units (assuming a SD of 15) and taking into account anticipated mortality, with 90% power and a two-sided 5% level of significance, a target sample size of 1400 infants was required (Section 2, Appendix).[21] Primary outcome analyses were by intention-to-treat. Outcomes were compared for all infants allocated to intervention or placebo, regardless of whether, or for how long, they received trial solutions.

Baseline characteristics were described by randomization allocation, using numbers with percentages for binary and categorical variables, and means and SD for continuous data. For

the three main domains of the Bayley-III, the difference in mean score between the iodide and placebo groups was assessed with the independent samples T test, using a 5% 2-sided significance level. No adjustment for multiple testing was planned, despite the multiplicity of primary outcome measures. If, for example, the results for each of the three main domains of the Bayley-III had been statistically significant, clinicians and parents alike would have assumed that the replication of effect was corroborating evidence of a genuine treatment effect. Therefore 'penalising' these effects statistically would be counter-intuitive. Likewise, if only one of the domains had been statistically significant, our interpretation would have been cautious.

The minimum Bayley-III score possible for each domain was assigned to deaths, and to infants too disabled to make assessment meaningful. This is contrary to the published protocol,[21] which referred only to deaths, and stated that 55 would be assigned to the main domains. However, analysis of preliminary data, blinded to allocation, showed that 8% of surviving infants scored lower than the arbitrary cut-off of 55 we had proposed, hence our decision to use the value at the bottom of the scale. The primary outcomes were also analysed for survivors only, in order to give a fair representation of the average ability of assessable children. (For further details about imputation of missing primary outcomes see Section 2, Appendix.) Secondary outcomes analyses were performed in survivors, although Bayley-III subtest scores are shown also for the intention-to-treat population. Comparative analyses used the odds ratio (OR) plus 99% confidence interval (CI) for dichotomous/categorical outcomes, or the mean difference (plus 99% CI) for normally distributed continuous outcomes.

Pre-specified sub-group analyses were performed using the F test for interaction for selected baseline (i.e. gestational age ≤25, 26-27, 28-30 weeks and maternal thyroid disease status) and other characteristics (the level of nursing care as a proxy for illness severity and infant

thyroxinemic status). Infants were classified as hypothyroxinemic if they had a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e. ≤25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; the remainder of infants were classified as euthyroid.

RESULTS

Between March 2010 and December 2012, 1275 infants were enrolled from 21 hospitals. Two infants were randomized in error and 14 parents withdrew consent for their infant's data to be used (Figure 1). Bayley-III assessments were available for 498/631 (79%) iodide and 499/628 (79%) placebo supplemented infants (Figure 1). Limited follow-up data were available for an additional 59/631 (9%) iodide and 48/628 (8%) placebo supplemented infants. At baseline, infant/maternal characteristics were very similar (Table 1).

Sixty-five (65/631, 10%) infants from the iodide group and 66 (66/628, 11%) infants from the placebo group died between randomization and the two year follow-up. The main causes of death in the intervention phase were necrotizing enterocolitis (31% in each group), followed by infection (iodide group 23%, placebo 20%) (Supplementary Table 2, Appendix). During the neonatal period, 11 infants were treated with Levo-thyroxine for variable durations and variable dosages (9 in the iodide arm, 2 in the placebo) and received a working clinical diagnosis of hypothyroidism. At two years of age, 13 infants (7 from the original 11, and 6 additional infants) were receiving Levothyroxine (8 iodide and 5 placebo); no infant was reported to have thyroid toxicity.

OUTCOMES

There was no significant difference between groups in the main domains of the Bayley-III: mean difference in Cognitive score, -0.34, 95% CI -2.57 to 1.89; in Motor composite score, 0.21, 95% CI -2.23 to 2.65; and in Language composite score, -0.05, 95% CI -2.48 to 2.39 (Table 2). There were no differences when the analyses were repeated for survivors, either unadjusted or adjusted

(Supplementary Table 3a-e, Appendix). Overall, the frequency of postnatal conditions was similar between the groups. The numbers of infants at each level of nursing care, the amount of parenteral nutrition (as a percentage of the total nutrition) at each postnatal measurement day, and the prescribed drug usage was the same in the iodide and placebo supplemented groups (Table 2, Supplementary Table 4, Appendix).

There were no significant differences between levels of T4 or TBG (Figure 2, Supplementary Figure 1, Appendix). Levels of TSH were generally slightly higher in the iodide arm, with significant differences evident at postnatal days 7 and 14 (Figure 2).

PRE-SPECIFIED SUB-GROUP ANALYSIS

The differences in mean Bayley-III scores between the iodide and placebo groups did not differ appreciably by gestational age-group or maternal thyroid disease status (Supplementary Figure 2); nor by neonatal illness, which was approximated by using the level of nursing care (Supplementary Figures 3a and b, Appendix). For the hypothyroxinemic subgroup (n=288) there was weak evidence of a treatment effect, which resulted in treated hypothyroxinemic infants having similar Bayley-III scores to euthyroid infants (Supplementary Table 5, Appendix). A test of interaction between the hypothyroxinemic and euthyroid groups was significant at the 5% level for the Language Composite Score and its subtest score Receptive Communication (Figure 3).

ADVERSE EVENTS

There were no SUSARs reported during the trial. Sixty adverse events were reported for the iodide group and 28 for the placebo group. Because some UK newborn screening laboratories instigate follow-up tests at TSH levels ≥6mU/l, we classified this level as an adverse event to ensure that these infants were investigated quickly by the local unit. The highest TSH level

recorded was an isolated value of 34 mU/L; such mildly raised TSHs were not considered clinically as an adverse event (Supplementary Table 6, Appendix).

DISCUSSION

The evidence from this large pragmatic trial shows no overall benefit of iodide supplementation on neurodevelopment, measured at two years, for preterm infants. The iodide supplemented group had slightly higher levels of TSH (but not T4 or TBG) than the placebo group. The trial shows no adverse consequences associated with iodide supplementation at 30μg/kg/day.

The results of the trial were unexpected and do not agree with the evidence from observational studies. The impetus for this trial was the accumulating evidence from observational studies that hypothyroxinemia is associated with compromised neurodevelopment.[15-20] In response to this evidence, some researchers explored the use of treatment with thyroxine[23,24] but there were insufficient data to determine whether treatment was beneficial. Only one study of thyroxine supplementation in preterm infants included long-term neurodevelopmental outcome and the results were equivocal.[23] In that study, infants receiving thyroxine supplementation (compared to placebo) scored 18 points higher aged two years on the Bayley-II Cognitive component, but only if they were <27 weeks gestation; supplemented infants born ≥27 weeks scored 10 points lower than non-supplemented infants. Subsequent follow-up at 5.7[25] and 10 years[26] confirmed these findings. Despite the equivocal results, a recent survey indicated that clinical treatment with thyroxine has increased 2.6 fold in neonates born <27 weeks' gestation.[27] Continuing clinical interest in hypothyroxinemia led to a phase 1 placebo-controlled trial of thyroxine with triiodothyronine therapy.[24] That trial showed changes in T4 with continuous supplement of low-dose thyroxine over 42 days, but no benefit of supplementation at three years of age in Bayley-III Cognitive score, albeit the study included very few infants.[28] In our trial the iodide arm

showed no difference in Bayley-III scores between infants classified as hypothyroxinemic and euthyroid, whereas in the placebo arm, the hypothyroxinemic group performed worse on the Bayley-III than the euthyroid group, especially in the language domain. This result suggests that hypothyroxinemia may not simply be an epiphenomenon of non-thyroidal illness. The results also suggest that iodide supplementation alone, at 30μg/kg/day, without the addition of T4 replacement therapy, can mitigate the adverse consequences of hypothyroxinemia. This is important because T4 replacement therapy may be harmful if it is given to infants who do not require it.[23]

Explanation of the neutral impact of iodide supplementation that we observe is hindered by the lack of iodide balance data, especially urinary iodide excretion. We considered monitoring urinary iodide during the active phase of the trial but concluded that the collection, storage, transport and analysis of these data would have been prohibitively costly. Instead, we relied upon the evidence base, which suggests that: preterm infants are vulnerable to iodide deficiency while on parenteral nutrition,[7,8] breast and formula milk provide highly variable amounts of iodide,[29] drugs and supplements typically given to neonates contain miniscule amounts of iodide,[8] and the UK population is mildly iodide deficient,[30,31] which exaggerates thyroid dysfunction.

The neutral effect of this trial has at least three possible explanations: first, the placebo infants received iodide from hitherto unknown iodine sources; second, the level of iodide supplementation was too low; and thirdly the Bayley-III is insufficiently sensitive. We do not believe that the infants in the placebo group were exposed to additional iodide. There are only two main sources of extraneous iodide that neonates are routinely exposed: topical iodide containing skin cleansers and variable quantities of free iodide from exposure to iodinated contrast media.[32] Any infant exposed to these sources during the I2S2 trial was immediately withdrawn from trial solutions. A study in 2012[33] reported that parenteral nutrition contained

almost no iodine and, with no evidence to the contrary, 1-3μg/kg/day[8] remains the best estimate of likely intake of the placebo group. The recommended level of iodide intake of 30-40μg/kg/day for preterm infants is based on balance data for healthy preterm infants at around one month of age.[7] It is conceivable that the trial supplement of 30μg/kg/day is too low an amount for sick, preterm neonates receiving parenteral nutrition, whose immature physiology may require higher amounts of nutrients relative to the term infant. The extra nutrient requirement of the extreme preterm infant has already been shown for other ions, where the fractional urinary excretion is high in the most extreme preterm infants, but with maturation of the kidney this declines.[14] It is also possible that 30μg/kg/day is too low for a mild-to-moderately iodine deficient population such as the UK. Future studies, such as the meticulous iodine balance study in term infants by Dold et al[34], are needed which examine the physiology of iodide metabolism in the developing fetus and preterm infant. Finally, the use of the Bayley-III scales as the primary outcome may have contributed to the neutral findings. The Bayley-III is a test of global neurodevelopment and it is possible that more targeted developmental tests incorporating, for example, visual acuity or autobiographical memory performance[35] may, in the future, identify differences between the groups.

Although it is not normally appropriate to investigate sub-group variables that could be affected by the trial intervention, we felt it was important to do so on this occasion and specified *a priori* and in our statistical analysis plan our intention. The only known human role for iodine is for the production of thyroid hormones and we hypothesized that the iodide intervention (but not the placebo) would positively affect the Bayley score via the intermediary of (increased) thyroid hormone with a concomitant decrease in the incidence of hypothyroxinemia. There is no evidence or plausible reason why iodide would have a direct or independent effect on the Bayley Score, and other factors which would contribute an

independent effect on the Bayley score would be equally distributed between the arms of the trial due to random allocation. Thus the typical confounders of interpretation are mitigated.

This trial has three findings. Iodide supplementation to all infants born <31 weeks' gestation confers no benefit to neurodevelopment measured by the Bayley-III scales at 2 years of age. Giving iodide at 30μg/kg/day was associated with no adverse consequences. Finally, there is only weak evidence that the sub-group of hypothyroxinemic infants gained benefit from iodide supplementation in one of three main Bayley-III domains. The gain was small and the clinical relevance of a gain of this magnitude is uncertain. But, if transient hypothyroxinemia is considered an important clinical entity, iodide supplementation of infants with low T4 levels may provide a pragmatic solution to mitigating the condition. The alternative is to supplement only those infants who are hypothyroxinemic; however, identifying infants with low T4 levels contemporaneously remains challenging.[36]

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We thank the parents and children who participated in this trial and the many NHS staff in UK hospitals who recruited, managed or received infants under the trial protocol.

STUDY OVERSIGHT

The trial was designed by the I2S2 co-investigators, oversight was provided by an independent Trial Steering Committee and independent Data Monitoring Committee. Data were collected by I2S2-trained nurses, and entered and verified in OpenClinica® by experienced data handlers in NPEU CTU. Trial solutions were manufactured by Torbay PMU, South Devon Healthcare NHS Foundation Trust with funds from the study; the company had no input to the trial design, conduct or analysis. The manuscript was written by the authors, who vouch for the accuracy and completeness of this report and for the fidelity of the report to the study protocol.

A full trial protocol is available at www.npeu.ox.ac.uk/i2s2

FIGURE LEGENDS

Figure 1: Trial profile

Figure 2: Differences in mean levels of T4 and log TSH between iodide and placebo groups by gestation at delivery and day of blood sampling

Figure 3: Differences in mean Bayley-III scores in survivors between iodide and placebo groups by infants' thyroid status

I2S2 COLLABORATIVE GROUP

I2S2 Trial team

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I2S2 nursing staff Julie Brown, Altnagelvin Area Hospital, Londonderry; Nicola McMonagle, Altnagelvin Area Hospital, Londonderry; Patrick Lawlor, Royal Maternity Hospital, Belfast; Fran Wootton, Birmingham City Hospital; Susan Whitehouse, Birmingham City Hospital; Lara Alamad, NIHR Clinical Research Network West Midlands; Jane Lovatt Birmingham Heartlands Hospital and NIHR Clinical Research Network West Midlands; Heather Barrow, Birmingham Women's Hospital; Michael Dixie, Birmingham Women's Hospital; Rachel Jackson, Birmingham Women's Hospital; Elizabeth Simcox, Birmingham Women's Hospital; Sarah Reynolds, University Hospital Coventry; Sue Dale, University Hospital Coventry; Vanessa Unsworth, Derbyshire Children's Hospital; Nicola Watson, Derbyshire Children's Hospital; Coral Smith, Derbyshire Children's Hospital; Ruth Ballington, Derbyshire Children's Hospital; Deirdre Plews, Ninewells Hospital and Medical School, Dundee; Lorna McKay the former Southern General Hospital and Princess Royal Hospital, Glasgow; Lorraine Herbert, University Hospital Crosshouse, Ayrshire; Liz Macrae, University Hospital Crosshouse, Ayrshire; Marie Hubbard, Leicester Royal Infirmary; Amanda Forster, James Cook University Hospital, Middleborough; Nicola Prosser, James Cook University Hospital; Tracy Davies, James Cook University Hospital, Middleborough; Steve Williamson ,Royal Victoria Infirmary, Newcastle; Wendy Cheadle, University Hospital of North Tees, Stockton-On-Tees; Helen Navara, City Hospital and Queen's Medical Centre, Nottingham; Yvonne Hooton, City Hospital and Queen's Medical Centre, Nottingham; Sue Hallett, Royal Berkshire Hospital, Reading; Julie Cook, Jessop Wing, Sheffield; Olwyn Major, Sunderland Royal Hospital; Avril McManus, Wishaw General Hospital.

Trial Steering Committee Independent members: Jane Norman (Chair) and James Boardman, University of Edinburgh; Joanne Rovet, University of Toronto; Fiona Douglas, University of Dundee; Sam Richmond*, Sunderland Royal Hospital; Morag Campbell, NHS Greater Glasgow. Non-independent members: Fiona Williams, Robert Hume, University of Dundee; Edmund Juszczak, University of Oxford; Peter Brocklehurst, University College London. Observers: Ursula Bowler, Kayleigh Stanbury (née Morgan), University of Oxford.

Data Monitoring Committee: The Data Monitoring Committee: Henry Halliday (Chair), Belfast; Christopher Kelnar and Gordon Murray, University of Edinburgh; Simon Ogston, University of Dundee.

* Very sadly Sam Richmond passed away during the trial on 10th March 2013.

NHS Staff in receiving hospitals In addition to the recruiting hospitals, a great many hospitals and NHS staff received I2S2 trial infants for temporary or permanent continuing care. Their help was invaluable and contributed appreciably to the smooth running and success of the trial.

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TABLE 1 Infant and Maternal Baseline Characteristics

Characteristic		Iodide[A] (N=631)	Placebo[A] (N=628)
Maternal age at delivery – yr (mean ±SD)		29.3 (±6.4)	29.4 (±6.5)
Maternal thyroid disease concurrent with pregnancy N (%)		22 (4)	19 (3)
Maternal steroids given for prevention of RDS[B] N (%)		586 (93)	569 (91)
Maternal steroids given for reasons other than RDS[B] N (%)		40 (6)	34 (5)
Smoking status N (%)	Current	150 (24)	139 (22)
	Ex-smoker	68 (11)	86 (14)
	Non	410 (65)	401 (64)
Analgesia given during delivery N (%) (women may have more than one type of pain relief)	None given	54 (9)	52 (8)
	Entonox (nitrous oxide)	220 (35)	234 (37)
	General anaesthesia	87 (14)	77 (12)
	Epidural/spinal block	273 (43)	260 (41)
	Opioid	100 (16)	115 (18)
	Other[C]	25 (4)	32 (5)
Mode of delivery N (%)			
	Spontaneous cephalic vaginal	221 (35)	237 (38)
	Vaginal breech	74 (12)	69 (11)
	Instrumental cephalic vaginal	11 (2)	14 (2)
	Elective caesarean	41 (6)	33 (5)
	Emergency caesarean	284 (45)	275 (44)
Region of birth N (%)	Scotland	140 (22)	135 (22)
	North East England	183 (29)	183 (29)
	Remainder England	263 (42)	264 (42)
	Northern Ireland	45 (7)	46 (7)
Infant ancestry N (%)	Black	16 (3)	23 (4)
	Asian	48 (8)	43 (7)
	White	531 (84)	516 (82)
	Other	35 (6)	45 (7)
Main cause of preterm birth N (%)			
	Pre-labour rupture of membranes (PROM)	173 (27)	183 (29)
	Preterm labour without PROM	215 (34)	201 (32)
	Antepartum haemorrhage (APH)	66 (10)	60 (10)
	Pregnancy induced hypertension ± APH	54 (9)	68 (11)
	Other maternal illness	55 (9)	58 (9)
	Poor fetal growth	67 (11)	56 (9)
	Other reason	1 (<1)	2 (<1)
Infant sex N (%)	Male	349 (55)	347 (55)
	Female	282 (45)	281 (45)
Multiple birth N (%)	Singleton	450 (71)	454 (72)
	Twin	160 (25)	151 (24)
	Triplet	21 (3)	23 (4)
Gestational age – wk (mean ±SD)		27.4 (±2.0)	27.4 (±2.0)
Birth weight – g (mean ±SD)		1,055 g (±308)	1,053 g (±309)
Apgar score at 5 mins (mean ±SD)		7.8 (±1.8)	7.8 (±1.8)
Age at receipt of first trial solution – hr:min (mean ± SD)		39:20 (±15:09)	39:02 (±13:46)

[A] 8 infants from the placebo group and 6 infants from the iodide group were withdrawn from the trial by their parents who would not allow their data to be used (see Figure 1).

[B] RDS denotes Respiratory Distress Syndrome

[C] The majority of other is codeine/paracetamol (iodide 19/25, placebo 22/32)

Percentages only add to 100% when there are no missing data.

There were no significant differences between the groups for any variables. SD denotes standard deviation

TABLE 2 Primary and Secondary Outcomes

Outcomes		Iodide N=631	Placebo N=628	Mean difference (Iodide – placebo)	95% CI (P value)
Primary outcomes (mean ± SD) (intention-to-treat population)[A]					
Bayley-III Cognitive score		88.9 ± 19.2	89.2 ± 19.5	-0.34	-2.57 to 1.89 (0.77)
Bayley-III Motor composite score		88.2 ± 21.0	88.0 ± 21.6	0.21	-2.23 to 2.65 (0.87)
Bayley-III Language composite score		85.1 ± 21.7	85.2 ± 21.8	-0.05	-2.48 to 2.39 (0.97)
Secondary outcomes Bayley-III subtests (mean ± SD) (intention-to-treat population)[B]					**99% CI**
Receptive Communication		7.51 ± 3.80	7.46 ± 3.77	0.05	-0.51 to 0.61
Expressive Communication		7.31 ± 4.06	7.34 ± 4.06	-0.02	-0.62 to 0.57
Fine Motor		8.86 ± 3.99	8.72 ± 4.13	0.15	-0.47 to 0.76
Gross Motor		7.07 ± 3.61	7.16 ± 3.68	-0.09	-0.63 to 0.45
Low score in any main Bayley domain (i.e. Cognitive, Motor, Language) N (%) (intention-to-treat population)[A]					**Odds ratio (99% CI)**
≥ 85		305.7 (48)	319.6 (51)		1.10 (0.82 to 1.49)
<85 (or death)		325.3 (52)	308.4 (49)		
Postnatal infant conditions N (%) (survivors only)		**N=629[C]**	**N=628**		**Odds ratio (99% CI)**
Respiratory distress syndrome		591 (94)	581 (93)		1.26 (0.70 to 2.25)
Chronic lung disease		262 (42)	235 (37)		1.19 (0.89 to 1.61)
Persistent ductus arteriosus		192 (31)	195 (31)		0.98 (0.71 to 1.34)
Necrotizing enterocolitis		128 (20)	103 (16)		1.30 (0.89 to 1.90)
Hyperbilirubinemia		522 (83)	519 (83)		1.03 (0.70 to 1.51)
Infants with ≥ 1 acquired infections		283 (45)	258 (41)		1.03 (0.92 to 1.16)
Cerebral pathology closest to 34 weeks					0.94 (0.62 to 1.44)[D]
Porencephalic cyst		9 (1)	7 (1)		
Cystic periventricular leukomalacia		13 (2)	12 (2)		
Ventriculomegaly		27 (4)	38 (6)		
Miscellaneous		37 (6)	26 (4)		
More than one pathology		7 (1)	6 (1)		Reference category
No abnormalities detected		385 (61)	392 (62)		
Missing data		153 (24)	147 (23)		
Hearing and Vision impairment in survivors only N (%)					**Odds ratio (99% CI)**
Deaf or requires hearing aids		15/551 (3)	14/542 (3)		1.06 (0.40 to 2.79)
Blind or difficulty seeing even with glasses		9/551 (2)	14/541 (3)		0·63 (0.21 to 1.90)
Level of Nursing Care in survivors only N (%)					
		N=613[E]	**N=615[E]**		**Odds ratio (99% CI)**
Postnatal day 7	Level 1	323 (51)	321 (51)		1.01 (0.85 to 1.20)
	Level 2	206 (33)	212 (34)		1.03 (0.86 to 1.23)
	Level 3	84 (13)	82 (13)		Reference category
		N=598	**N=596**		
Postnatal day 14	Level 1	230 (37)	219 (35)		1.05 (0.90 to 1.22)
	Level 2	200 (32)	230 (37)		1.15 (0.99 to 1.33)
	Level 3	168 (27)	147 (23)		Reference category
		N=583	**N=577**		
Postnatal day 28	Level 1	137 (22)	131 (21)		1.01 (0.86 to 1.17)
	Level 2	216 (34)	228 (36)		1.06 (0.93 to 1.20)
	Level 3	230 (37)	218 (35)		Reference category
		N=564	**N=569**		
34 corrected weeks' gestation	Level 1	39 (6)	33 (5)		0.89 (0.69 to 1.16)
	Level 2	188 (30)	181 (29)		0.96 (0.84 to 1.09)
	Level 3	337 (53	355 (57)		Reference category
Parenteral nutrition as a percentage of total nutrition mean % ± SD (N[F]) In survivors only				**Mean difference**	**(99% CI)**
Postnatal day 7		57.1 ± 37.0 (613)	57.2 ± 37.2 (613)	-0.11	-5.58 to 5.36
Postnatal day 14		23.9 ± 37.5 (597)	24.0 ± 37.0 (595)	-0.11	-5.68 to 5.46
Postnatal day 28		13.5 ± 31.0 (575)	13.2 ± 30.6 (575)	0.26	-4.42 to 4.95
34 corrected weeks' gestation		8.8 ± 26.1 (558)	8.4 ± 24.9 (565)	0.38	-3.55 to 4.30

[A] Intention-to-treat population includes: deaths & severely disabled infants which were coded 55 for the Cognitive score, 47 for the Language composite score and 46 for the Motor composite score. Missing outcomes for losses to follow-up and for infants who were withdrawn but allowed their data to be used were imputed

[B] In the four Bayley-III subtest scores deaths were scored as 1 or 0, reflecting their minimum scores.

[C] Two infants had no postnatal data collection forms
[D] The odds ratio was any cerebral pathology compared to no cerebral pathology
[E] N varies due to deaths or to infant withdrawals
[F] N varies due to deaths, infant withdrawals and missing data

FIGURE 1: Trial Profile

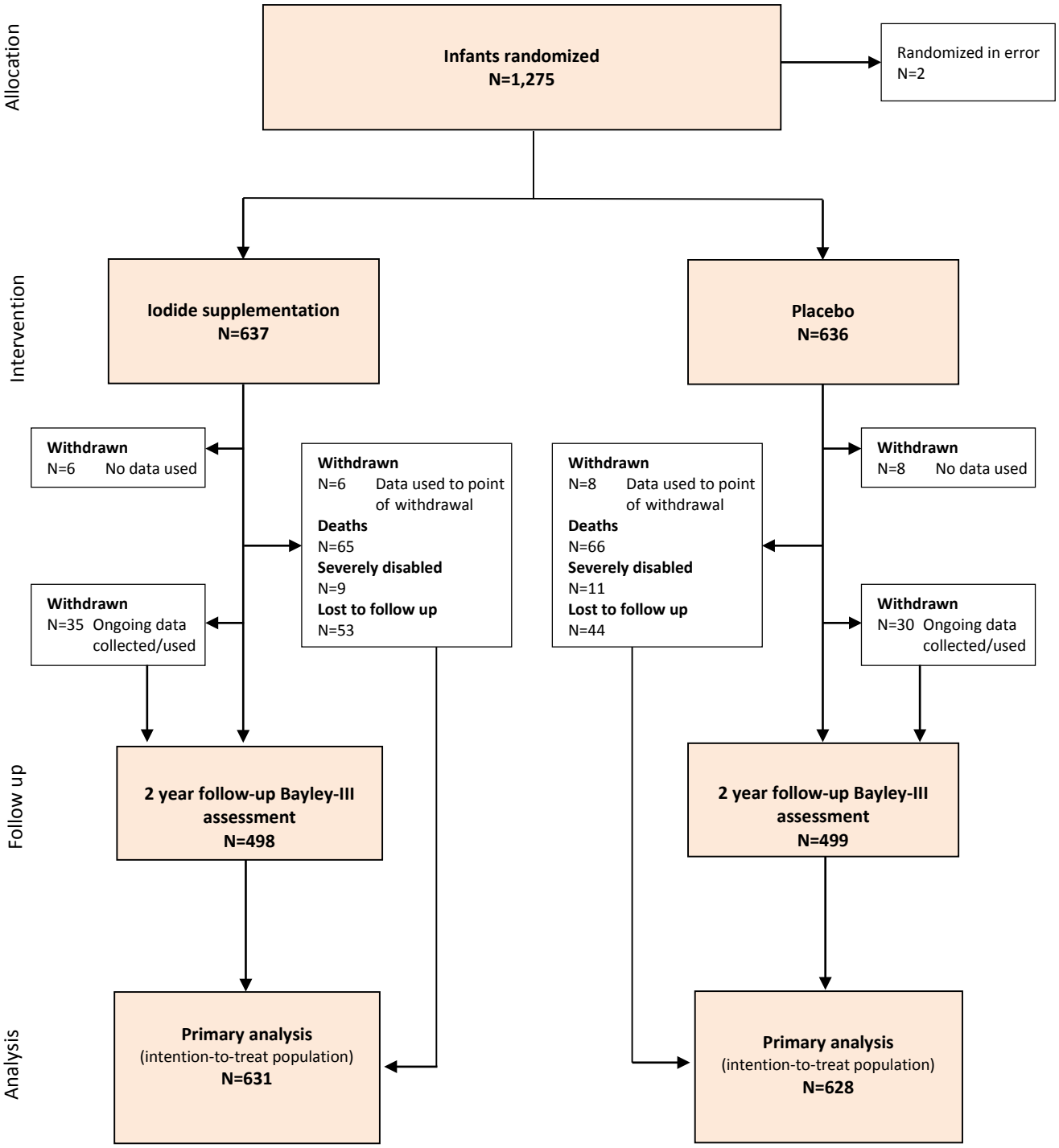
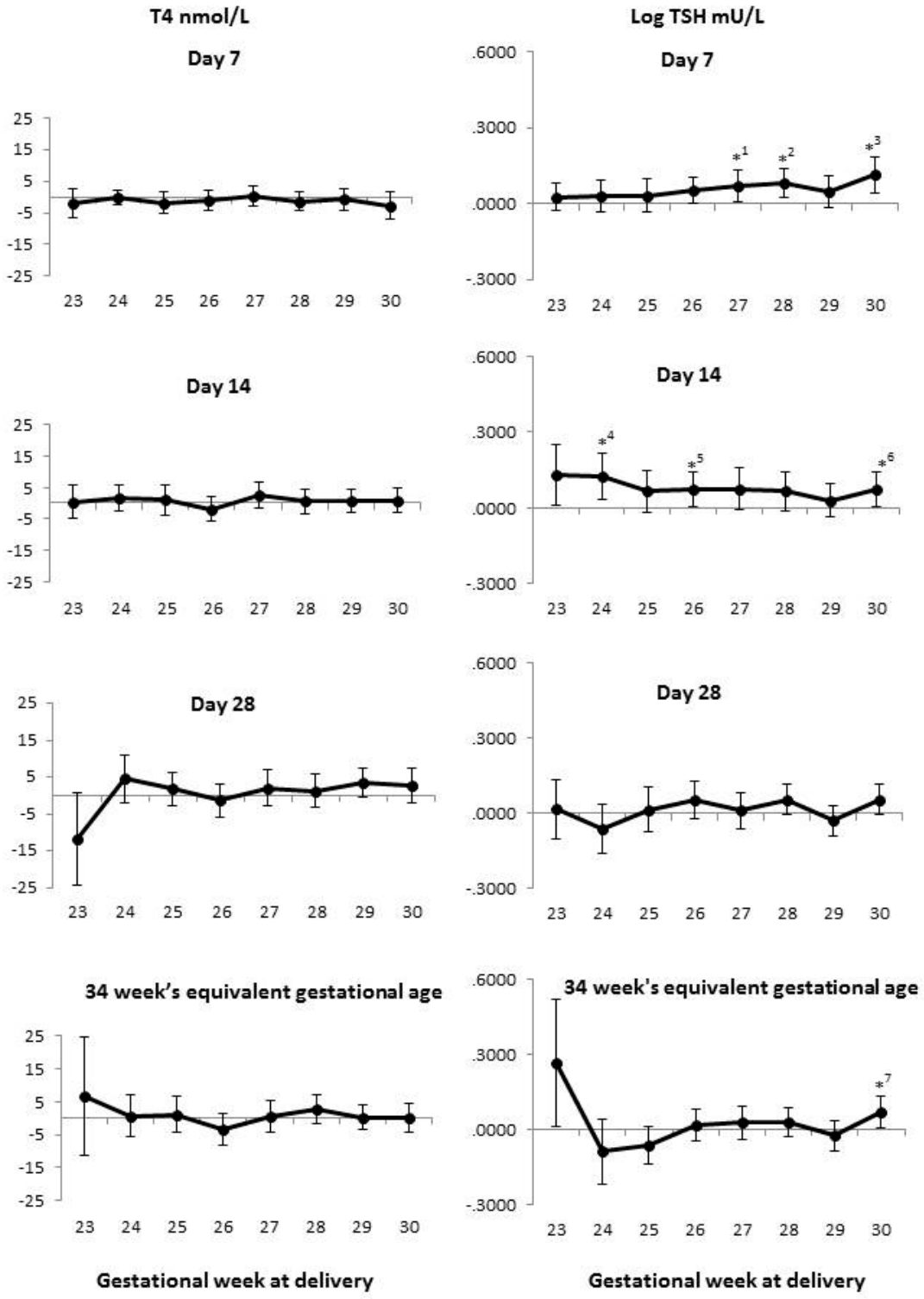


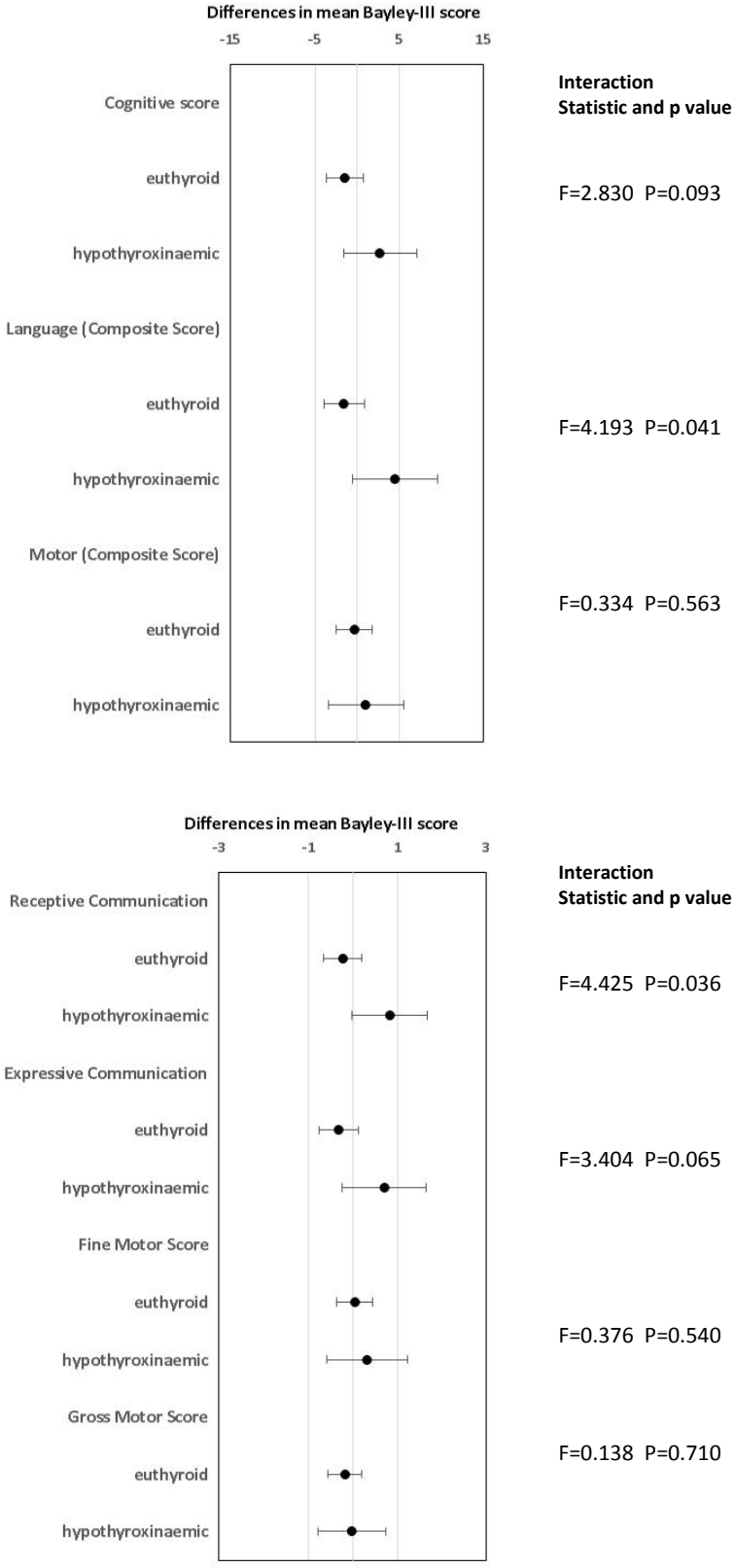
FIGURE 2: Differences in Mean Levels of T4 and log TSH between Iodide and Placebo Groups by Gestation at Delivery and Day of Blood Sampling



Error bars ±2 standard errors *[1] p=0.03 *[2] p=0.007 *[3] p=0.002 *[4] p=0.011 *[5] p= 0.035 *[6] p=0.046 *[7] p=0.033

Negative numbers indicate that the iodide group had lower levels of T4 or TSH than the placebo group
Positive numbers indicate that the iodide group had higher levels of T4 or TSH than the placebo group

FIGURE 3: Differences in Mean Bayley-III Scores in survivors[A] between Iodide and Placebo Groups by Infants' Thyroid Status



[A] infants who actually had a Bayley-III assessment (i.e. excludes imputed data)

APPENDIX I2S2

CONTENTS

SECTION 1, SUPPLEMENTARY TABLES AND FIGURES

SUPPLEMENTARY TABLE 0 Infants recruited by week of gestation

Gestational age (number and %)	Iodide		Placebo	
22 weeks	1	(0.2%)	1	(0.2%)
23 weeks	12	(1.9%)	14	(2.2%)
24 weeks	49	(7.8%)	47	(7.5%)
25 weeks	70	(11.1%)	71	(11.3%)
26 weeks	83	(13.2%)	74	(11.8%)
27 weeks	83	(13.2%)	91	(14.5%
28 weeks	109	(17.3%)	115	(18.3%)
29 weeks	112	(17.7%)	112	(17.8%)
30 weeks	112	(17.7%)	103	(16.4%)

SUPPLEMENTARY TABLE 1 Definitions of Postnatal Illnesses Recorded

Condition/illness/term	Definition
Postnatal conditions	
Respiratory distress syndrome	*Requiring oxygen with or without ventilatory support*
Pneumothorax	*Present if air leak on chest x-ray with or without treatment*
Pulmonary interstitial emphysema	*Radiological changes seen*
Pulmonary haemorrhage	*Fresh blood in ET, thought not to be due to trauma*
Chronic lung disease	*Receiving supplemental oxygen at equivalent of 36 weeks' gestation*
Cerebral pathology – closest to 34 corrected weeks	• *No abnormalities detected* • *Porencephalic cyst* • *Cystic periventricular leukomalacia* • *Ventriculomegaly* • *Cerebral atrophy*
Persistent ductus arteriosus	*Requiring treatment with any of the following: fluid restriction and diuretics with or without surgery or indomethacin*
Necrotizing enterocolitis	*Requiring treatment with TPN and ≥7 days antibiotic therapy, and/or surgery*
Retinopathy of prematurity	Requiring treatment
Congenital anomalies	
Hyperbilirubinaemia	Requiring treatment – highest level recorded
Meningitis	Confirmed by positive culture
Infection	Symptomatic infant with positive culture of blood, cerebrospinal fluid, or other normally sterile site, and with haematological markers of infection including one or more of the following: raised CRP, high or low white blood cell count, thrombocytopenia
Level of Nursing Care – The BAPM[A] score Level 1	Ventilated babies up to 24 hours post ventilation; receiving CPAP & <5 days old; <1,000 grams & receiving CPAP (plus 24 hrs after withdrawal); <29 weeks (first 48 hrs); emergency surgery pre- and post-operation (first 48 hrs); full exchange transfusion, peritoneal dialysis, IV's required for circulatory support/pulmonary vasodilator/prostaglandin (plus 24 hrs after withdrawal); instability requiring 1:1 care; care of the terminally ill on the day of death.
Level 2	CPAP; <1,000g; TPN; convulsions; O_2 therapy & <1,500g; Neonatal Abstinence Therapy; I/A lines/chest drains; partial exchange transfusion; tracheostomy care until supervised by parent; requiring frequent stimulation for severe apnoea.
Level 3	Special care is provided for all other infants who could not reasonably be expected to be looked after at home by their mother

[A] British Association of Perinatal Medicine. Standards for hospitals providing neonatal intensive and high dependency care. London: British Association of Perinatal Medicine, 2001.

SUPPLEMENTARY TABLE 2 Cause of Death during the Intervention Phase of the Trial

Event (number and %)	Iodide		Placebo	
Congenital anomaly[A]	0		0	
Pulmonary immaturity[B]	3	(5)	3	(5)
Hyaline membrane disease[C]	0		2	(3)
Hyaline membrane disease with intraventricular haemorrhage or infarction[C]	6	(10)	3	(5)
Hyaline membrane disease with infection[C]	2	(3)	1	(2)
Intraventricular haemorrhage[D]	3	(5)	4	(7)
Infection[E]	14	(23)	12	(20)
Necrotizing enterocolitis	19	(31)	18	(31)
Late sequelae of ventilation[F]	1	(2)	2	(3)
Miscellaneous	13	(21)	14	(24)
Total[G]	61	(9.7%)	59	(9.4%)

[A] Congenital Anomaly: any genetic or structural defect arising at conception or during embryogenesis incompatible with life or potentially treatable but causing death.

[B] Pulmonary Immaturity: structural immaturity of the lung so gross as to render sustained ventilatory support unsatisfactory from the outset.

[C]Hyaline membrane disease (HMD): death due to pulmonary immaturity or surfactant deficiency. Specify if there was co-existing significant periventricular or intraventricular bleeding (or infarction) or secondary infection.

[D]Intracranial haemorrhage: deaths due to intraventricular and periventricular haemorrhage should be separated from those due to other intracerebral haemorrhage (such as subdural and subarachnoid bleeding). Exclude intraventricular and periventricular haemorrhage associated with significant HMD.

[E]Infection: include antepartum and postpartum infection, but if there was infection associated with severe HMD, record this as defined previously.

[F]Late sequelae of ventilation: death due to progressive respiratory failure after one week of age without an acute precipitating cause. This should include babies dying with classic bronchopulmonary dysplasia after 28 days.

[G]The numbers of deaths in this table are those recorded during the intervention phase of the trial; the numbers are lower than those shown in Figure 1 of the paper as that figure includes deaths which occurred between the end of the intervention phase and the two year follow up.

SUPPLEMENTARY TABLE 3a Unadjusted and Adjusted Analyses of Primary and Secondary Outcomes: Difference in Bayley Scores between the Iodide compared to the Placebo group in Surviving Infants (N=498 iodide, N=499 placebo group)

OUTCOMES	UNADJUSTED (SCORES (95% CI)	ADJUSTED SCORES[A] (95% CI)
Primary outcomes		
Cognitive score	-0.67 (-2.62 to 1.28)	-0.60 (-2.49 to 1.29)
Motor composite score	-0.14 (-2.07 to 1.79)	-0.04 (-1.87 to 1.80)
Language composite score	-0.42 (-2.62 to 1.78)	-0.38 (-2.50 to 1.74)
Secondary Outcomes	Unadjusted scores (99% CI)	Adjusted scores[A] (99% CI)
Expressive communication scaled score	-0.13 (-0.66 to 0.40)	-0.10 (-0.62 to 0.41)
Receptive communication scaled score	-0.03 (-0.54 to 0.49)	-0.03 (-0.53 to 0.47)
Fine motor scaled score	0.08 (-0.42 to 0.58)	0.12 (-0.35 to 0.60)
Gross motor scaled score	-0.16 (-0.60 to 0.28)	-0.16 (-0.59 to 0.27)

[A]adjusted for the factors used at minimisation (i.e. infant gender, centre of randomization, gestation at delivery) and Bayley assessor

SUPPLEMENTARY TABLE 3b Unadjusted and Adjusted Analyses of Primary and Secondary Outcomes: Difference in Bayley Scores between the Iodide compared to the Placebo group in Surviving Infants, excluding those with additional exposure to iodide (N=468 iodide group, N=469 placebo)

OUTCOMES	UNADJUSTED SCORES (95% CI)	ADJUSTED SCORES[A] (95% CI)
Primary outcomes		
Cognitive score	-0.69 (-2.67 to 1.28)	-0.65 (-2.56 to 1.27)
Motor composite score	-0.41 (-2.34 to 1.52)	-0.39 (-2.23 to 1.46)
Language composite score	-0.20 (-2.45 to 2.04)	-0.25 (-2.43 to 1.93)
Secondary Outcomes	Unadjusted scores (99% CI)	Adjusted scores[A] (99% CI)
Expressive communication scaled score	-0.07 (-0.61 to 0.47)	-0.06 (-0.59 to 0.47)
Receptive communication scaled score	-0.01 (-0.53 to 0.52)	-0.03 (-0.54 to 0.49)
Fine motor scaled score	0.05 (-0.45 to 0.56)	0.07 (-0.41 to 0.55)
Gross motor scaled score	-0.22 (-0.66 to 0.22)	-0.23 (-0.66 to 0.21)

[A]adjusted for the factors used at minimisation (i.e. infant gender, centre of randomization, gestation at delivery) and Bayley assessor

SUPPLEMENTARY TABLE 3c Unadjusted and Adjusted Analyses of Primary and Secondary Outcomes: Difference in Bayley Scores between the Iodide compared to the Placebo group in all Randomized Infants[A] (N=631 iodide group, N=628 placebo)

Outcomes	UNADJUSTED SCORES (95% CI)	ADJUSTED SCORES[B] (95% CI)
Primary outcomes		
Cognitive score	-0.34 (-2.56 to 1.89)	-0.36 (-2.39 to 1.68)
Motor composite score	0.21 (-2.23 to 2.64)	0.22 (-1.98 to 2.43)
Language composite score	-0.05 (-2.48 to 2.39)	-0.07 (-2.32 to 2.17)
Secondary Outcomes	Unadjusted scores (99% CI)	Adjusted scores[B] (99% CI)
Expressive communication scaled score	-0.02 (-0.62 to 0.57)	-0.01 (-0.56 to 0.53)
Receptive communication scaled score	0.05 (-0.51 to 0.61)	0.04 (-0.49 to 0.57)
Fine motor scaled score	0.15 (-0.47 to 0.76)	0.16 (-0.41 to 0.72)
Gross motor scaled score	-0.09 (-0.63 to 0.45)	-0.10 (-0.60 to 0.40)

[A] i.e. by intention to treat which includes survivors, deaths, too disabled for assessment and lost to follow up

[B]adjusted for the factors used at minimisation (i.e. infant gender, centre of randomization, gestation at delivery) and Bayley assessor

SUPPLEMENTARY TABLE 3d Unadjusted Analysis of the Primary and Secondary Outcomes showing the Mean, and Differences between the Mean, of the Bayley-III Scores for Infants who Attended for Assessment and Including Single Imputation for Deaths and Disabled Infants

Outcomes	Iodide	Placebo	Mean difference (Iodide – placebo)	95% CI (P value)
Primary outcomes (mean ± SD, n)				
Bayley-III Cognitive score	88.2 ± 19.4 (572)	88.7 ± 19.8 (576)	-0.42	-2.69 to 1.85 (0.72)
Bayley-III Motor composite score	87.6 ± 21.4 (571)	87.5 ± 22.0 (576)	0.07	-2.44 to 2.59 (0.95)
Bayley-III Language composite score	84.6 ± 22.0 (572)	84.7 ± 22.1 (574)	-0.16	-2.71 to 2.40 (0.90)
Secondary outcomes (mean ± SD, n)				**99% CI**
Bayley-III subtests				
Receptive language	7.40 ± 3·85 (572)	7.39 ± 3.82 (574)	0.01	-0.57 to 0.60
Expressive language	7.17 ± 4.11 (572)	7.24 ± 4.13 (573)	-0.07	-0.70 to 0.56
Fine motor	8.73 ± 4.05 (571)	8.62 ± 4.21 (575)	0.11	-0.52 to 0.74
Gross motor	6.97 ± 3.69 (572)	7.07 ± 3.74 (575)	-0.10	-0.67 to 0.47
Low Bayley score in any main domain (cognitive, motor, language) (number and %)				**Odds ratio (99% CI)**
≥ 85	286 (50)	301 (52)		1.10 (0.81 to 1.48)
<85 (or death)	286 (50)	275 (48)		

SUPPLEMENTARY TABLE 3e Unadjusted Analysis of the Primary and Secondary Outcomes showing the Mean, and Differences between the Mean, of the Bayley-III Scores for Infants who Attended for Assessment (Excluding Single Imputation for Deaths and Disabled Infants)

Outcomes	Iodide	Placebo	Mean difference (Iodide – placebo)	95% CI (P value)
Primary outcomes (mean ± SD, n)				
Bayley-III Cognitive score	93.2 ± 15.6 (498)	93.8 ± 15.8 (499)	-0.67	-2.62 to 1.28 (0.50)
Bayley-III Motor composite score	93.8 ± 15.1 (497)	93.9 ± 15.9 (499)	-0.14	-2.07 to 1.79 (0.89)
Bayley-III Language composite score	90.2 ± 17.7 (498)	90.6 ± 17.6 (497)	-0.42	-2.62 to 1.78 (0.71)
Secondary outcomes (mean ± SD, n)				**99% CI**
Bayley-III subtests				
Receptive language	8.35 ± 3.17 (498)	8.38 ± 3.09 (497)	-0.03	-0.54 to 0.49
Expressive language	8.24 ± 3.26 (498)	8.37 ± 3.21 (498)	-0.13	-0.66 to 0.40
Fine motor	9.89 ± 2.93 (497)	9.80 ± 3.17 (498)	-0.08	-0.42 to 0.58
Gross motor	8.00 ± 2.71 (498)	8.16 ± 2.69 (498)	-0.16	-0.60 to 0.28
Low Bayley score in any main domain (cognitive, motor, language) (number and %)				**Odds ratio (99% CI)**
≥ 85	286 (57)	301 (60)		1.13 (0.81 to 1.57)
<85	212 (43)	198 (40)		

SUPPLEMENTARY TABLE 4 Comparison of Prescribed Drug Usage between the Iodide and the Placebo Supplemented Group

	Iodide Yes/No	Placebo Yes/No	Odds ratio (99%)
Day 7 postnatal	**n=613**	**n=615**	
Dexamethasone	3/610	2/613	1.51 (0.14 to 15.90)
Morphine/Diamorphine	83/530	81/534	1.03 (0.67 to 1.59)
Caffeine	501/112	498/117	1.05 (0.72 to 1.53)
Dopamine	27/586	20/595	1.37 (0.63 to 2.97)
Metronidazole	30/583	34/581	0.88 (0.45 to 1.71)
Dobutamine	13/600	15/600	0.87 (0.32 to 2.33)
Indomethacin	4/609	6/609	0.67 (0.13 to 3.54)
Day 14 postnatal	**n=597**	**n=596**	
Dexamethasone	4/593	2/594	2.00 (0.21 to 18.74)
Morphine/Diamorphine	62/535	58/538	1.08 (0.66 to 1.77)
Caffeine	484/113	483/113	1.00 (0.69 to 1.47)
Dopamine	9/588	8/588	1.13 (0.32 to 3.97)
Metronidazole	31/566	23/573	1.36 (0.66 to 2.82)
Dobutamine	6/591	4/592	1.50 (0.28 to 7.98)
Indomethacin	3/594	4/592	0.75 (0.10 to 5.38)
Day 28 postnatal	**n=582**	**n=578**	
Dexamethasone	18/564	27/551	0.65 (0.29 to 1.45)
Morphine/Diamorphine	43/539	48/530	0.88 (0.50 to 1.55)
Caffeine	384/198	393/185	0.91 (0.66 to 1.26)
Dopamine	7/575	4/574	1.75 (0.35 to 8.84)
Metronidazole	22/560	23/555	0.95 (0.43 to 2.08)
Dobutamine	3/579	3/575	0.99 (0.12 to 8.18)
Indomethacin	2/580	0/578	-
34 weeks equivalent gestational age	**n=564**	**n=569**	
Dexamethasone	10/554	13/556	0.77 (0.26 to 2.31)
Morphine/Diamorphine	19/545	13/556	1.49 (0.58 to 3.82)
Caffeine	306/258	297/272	1.09 (0.80 to 1.48)
Dopamine	4/560	2/567	2.03 (0.22 to 18.95)
Metronidazole	15/549	8/561	1.92 (0.61 to 5.98)
Dobutamine	1/563	1/568	1.01 (0.03 to 38.66)
Indomethacin	0/564	0/569	-

Change in denominator (n) is due to deaths, infants withdrawn, infants discharged home or missing data.

SUPPLEMENTARY TABLE 5 Hypothyroxinaemic status[A] and Bayley-III scores in survivors: mean ± standard deviation, (n)[B]

Sub-group	Bayley-III main domain scores			Bayley-III subset scores			
	Cognitive	Motor	Language	Receptive language	Expressive language	Fine motor	Gross motor
Euthyroid group							
iodide	94 ± 16 (389)	94 ± 15 (388)	91 ± 18 (389)	8.4 ± 3 (389)	8.3 ± 3 (389)	10.0 ± 3 (388)	8.1 ± 3 (389)
placebo	95 ± 15 (400)	95 ± 15 (400)	92 ± 17 (399)	8.7 ± 3 (399)	8.6 ± 3 (398)	9.9 ± 3 (399)	8.3 ± 3 (400)
T-test Iodide Versus Placebo p value α 99%	ns	ns	ns	ns	ns	ns	ns
Hypothyroxinemic group							
Iodide	92 ± 15 (107)	92 ± 15 (107)	89 ± 18 (17)	8.1 ± 3 (107)	8.1 ± 4 (107)	9.7 ± 3 (107)	7.6 ± 3 (107)
placebo	89 ± 18 (97)	91 ± 19 (97)	85 ± 19 (96)	7.3 ± 3 (96)	7.4 ± 3 (96)	9.3 ± 4 (97)	7.7 ± 3 (96)
T-test Iodide Versus Placebo p value α 99%	ns	ns	ns	ns	ns	ns	ns

[A] Infant thyroxinaemic status was classified as hypothyroxinaemia - a T4 level at or below the 10th percentile, corrected to gestational age subgroup (i.e =<25, 26-27, 28-30 weeks) on postnatal days 7, 14 or 28; euthyroid constituted the remainder

[B] This is a subgroup analysis, which was specified in the Statistical Analysis Plan

SUPPLEMENTARY TABLE 6 Trial Safety, SUSARs and Adverse Events

Event	Iodide	Placebo
SUSARs	0	0
ADVERSE EVENTS		
• **Incorrectly reported as a SAE**	2	0
• **TSH levels ≥6 mU/l identified on blood spot cards**		
Hypothyroidism *(specific diagnosis of congenital or transient hypothyroidism given OR no diagnosis mentioned but treated with levo-thyroxine)*	12[A]	2
Hypopituitarism	0	1
Thyroid function monitored *(or local endocrine policy followed)*	33	19
• **Miscellaneous** *(e.g. persistent metabolic acidosis, fluctuating sodium levels, intrahepatic calcification, hypernatremia, fulminating NEC, GI obstruction, abdominal mass, pleural effusion, clot in aorta, aortic sleeve thrombus, hypoglycemia)*	13	5
• **Hypopituitarism**	0	1

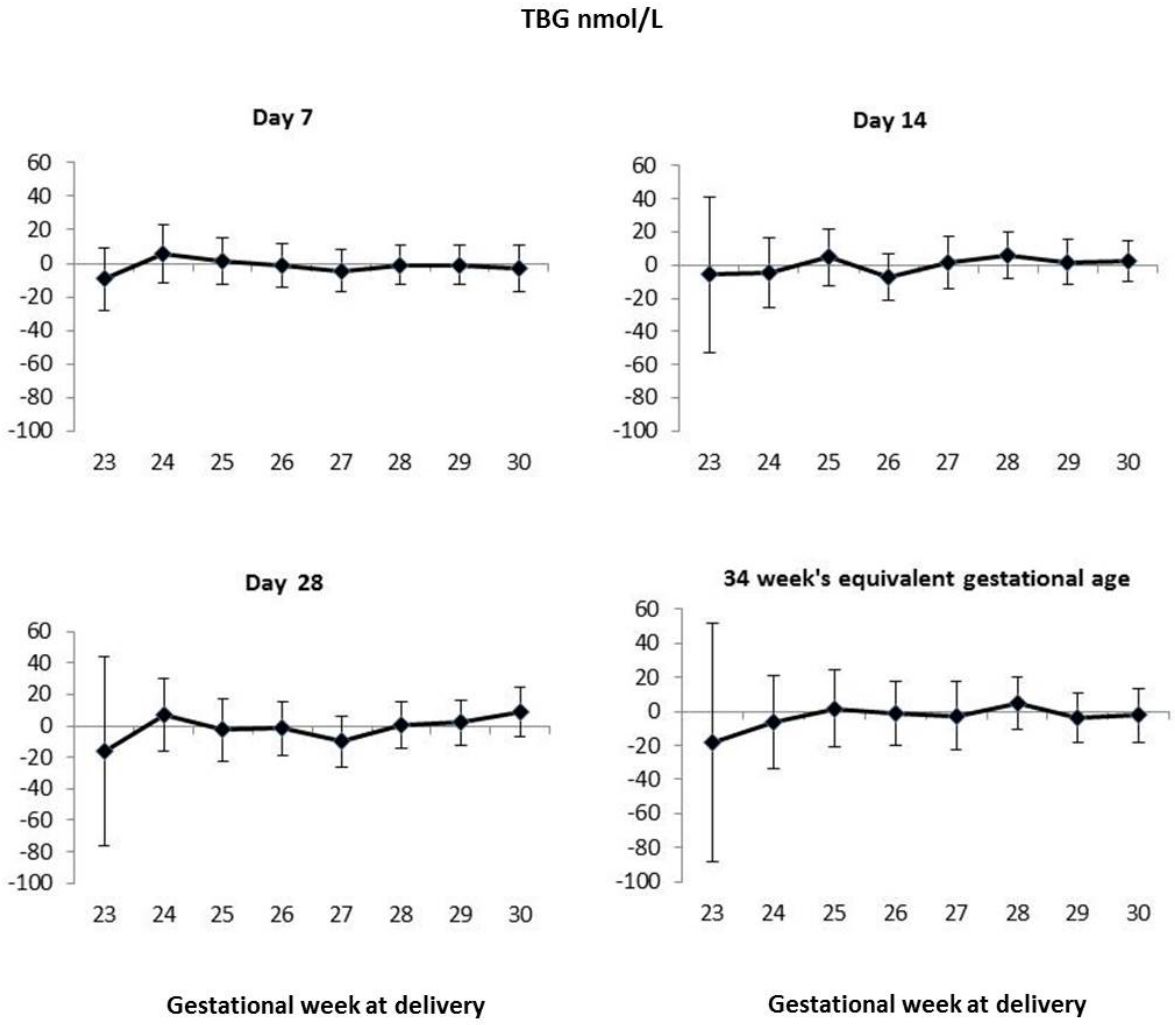
[A] Includes two cases of hyperthyroidism although TFTs indicative of hypothyroidism

The differences between the numbers in the intervention arm versus the placebo arm which reported hypothyroidism i.e. 12 versus 2, is statistically significant (Fisher Exact p=0.01). (The difference between the numbers who had TFTs monitored i.e. 33 versus 19 is not statistically significant.) This table reports adverse events that were reported to the trial team during the active phase of the trial (i.e. when infants were taking trial solutions). We encouraged a low threshold for reporting potential thyroid dysfunction. The thyroid hormone at which units started T4 replacement therapy was highly variable.

We followed up all infants who had a reported adverse event and during the neonatal period 11 infants were treated with Levo-thyroxine and received a conditional diagnosis of hypothyroidism; the numbers receiving Levo-thyroxine were 9 in the iodine arm and 2 in the placebo, Fisher Exact p=0.07.

The highest TSH level recorded was an isolated value of 34 mU/L.

SUPPLEMENTARY FIGURE 1 Difference in Mean Levels of TBG between Iodide and Placebo Groups by Gestation at Delivery and Day of Blood Sampling.

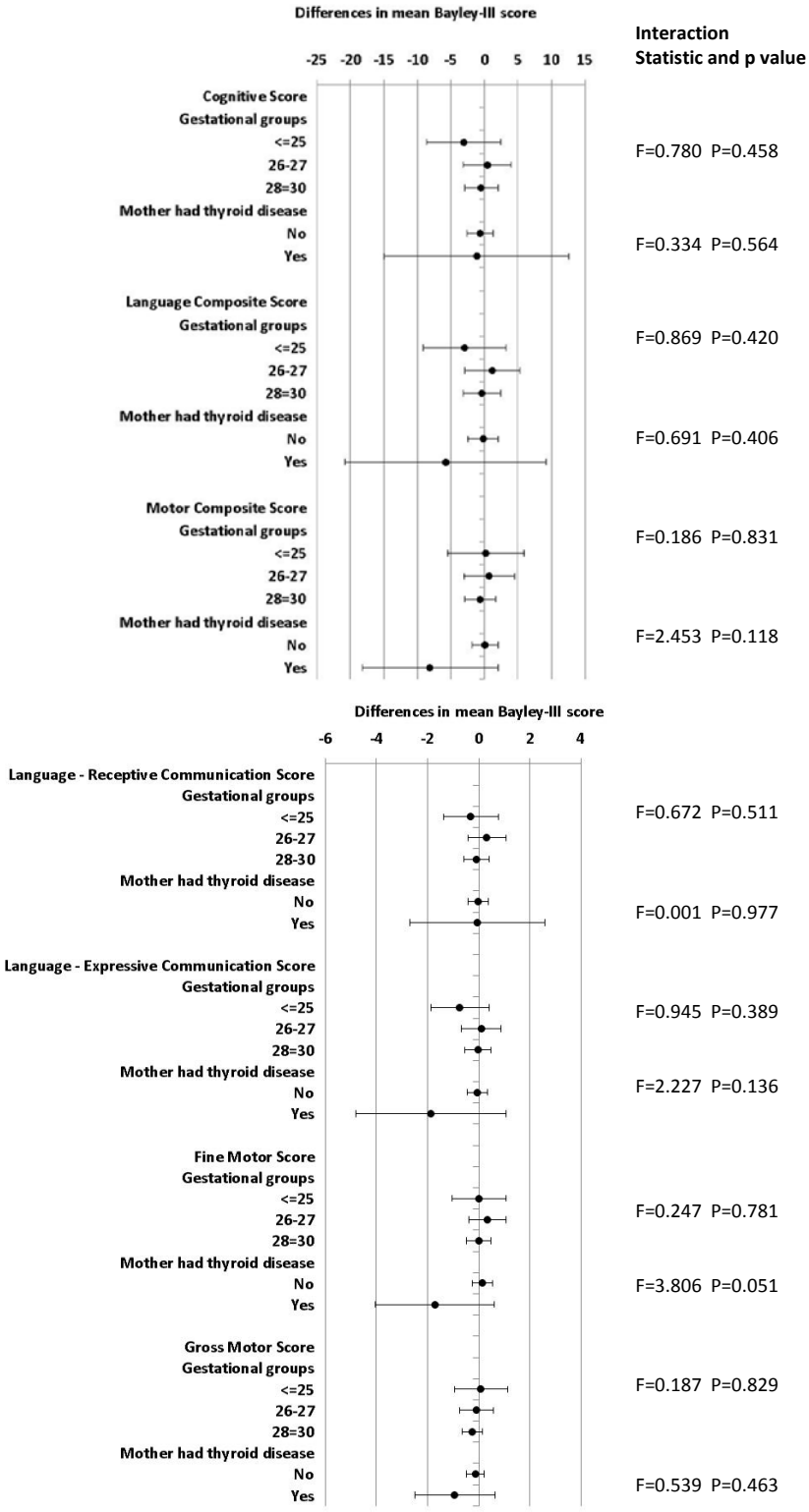


Error bars are ±2 standard errors of the mean

Negative numbers indicate that the iodide group had lower levels of TBG than the placebo group
Positive numbers indicate that the iodide group had higher levels of TBG than the placebo group

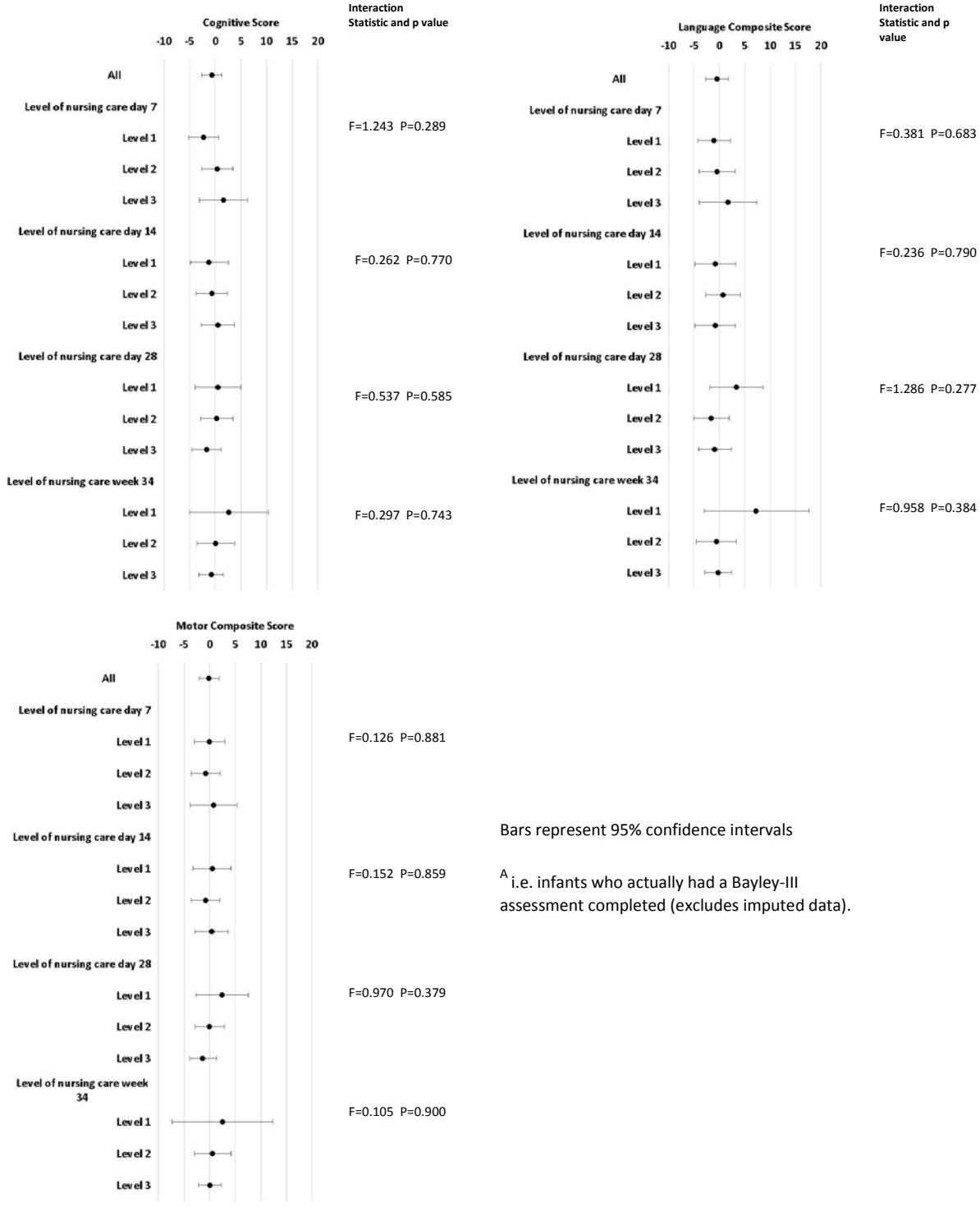
SUPPLEMENTARY FIGURE 2 Difference in Mean Bayley-III Scores in Survivors[A] Between the Iodide and Placebo Groups by Gestational Sub-group and Maternal Thyroid Status

SUPPLEMENTARY FIGURE 2 Difference in Mean Bayley-III Scores in Survivors[A] Between the Iodide and Placebo Groups by Gestational Sub-group and Maternal Thyroid Status



number of women with thyroid disease		iodide	placebo
	yes	22	19
	no	609	609

SUPPLEMENTARY FIGURE 3a Difference in Mean Bayley-III Scores in survivors[A] Between the Iodide and Placebo Groups, by Pre-specified Sub-group Analyses: Main Domains of the Bayley-III

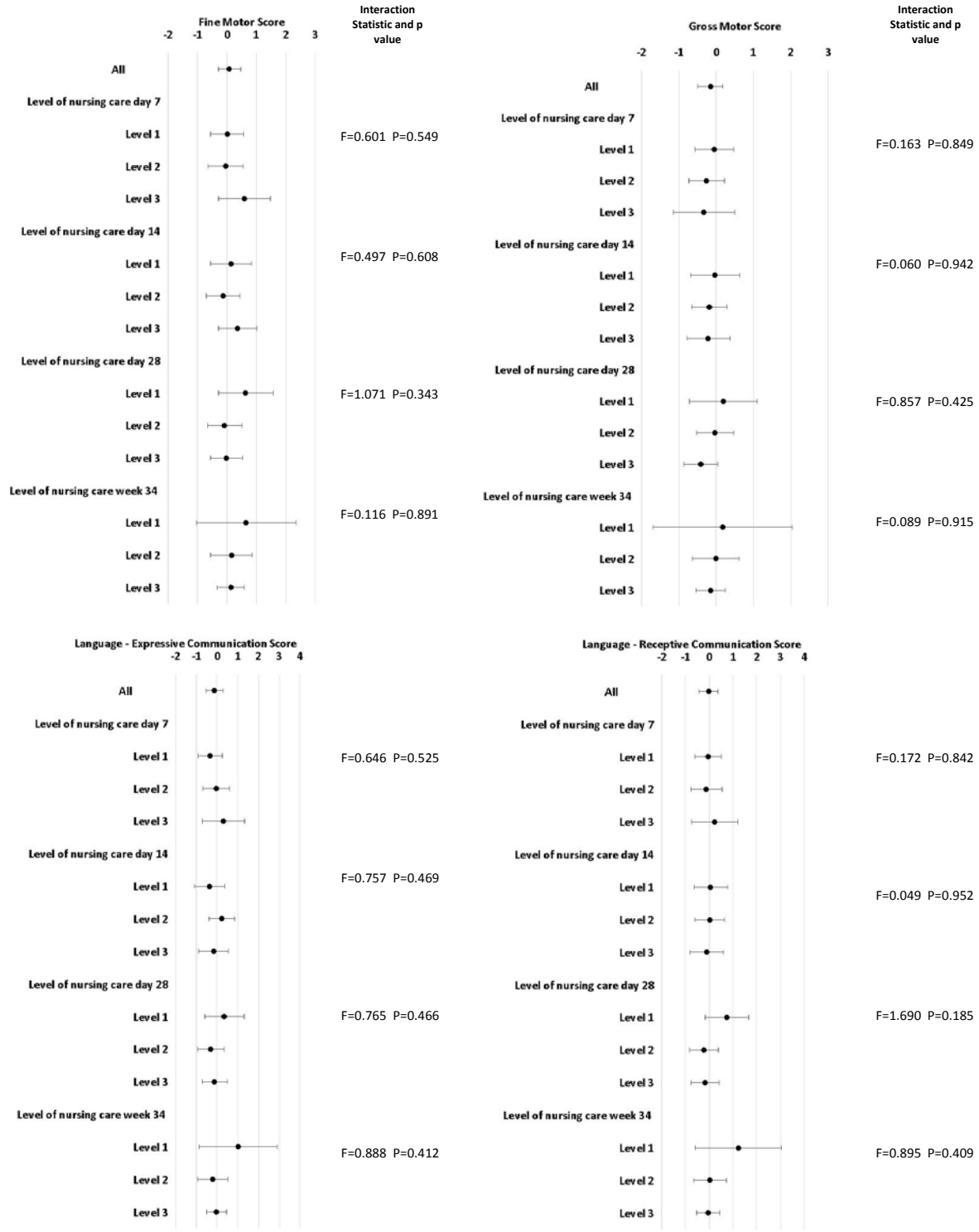


Bars represent 95% confidence intervals

[A] i.e. infants who actually had a Bayley-III assessment completed (excludes imputed data).

Negative scores indicate that the Iodide group performed worse than placebo group, positive scores that they performed better

SUPPLEMENTARY FIGURE 3b Difference in Mean Bayley-III Scores in Survivors[A] Between the Iodide and Placebo Groups, by Pre-specified Sub-group Analyses: Subtest Domains of the Bayley-III



Negative scores indicate that the Iodide group performed worse than placebo group, positive scores that they performed better

[A] i.e. infants who actually had a Bayley-III assessment completed (excludes imputed data).

Footnote to Supplementary Figure 3a and 3b. Care levels are a proxy for illness severity[9] (see Supplementary table 1 for definition).

SECTION 2, SAMPLE SIZE CALCULATION AND HANDLING OF MISSING BAYLEY-III OUTCOME SCORES

Sample Size Calculation

Assumptions:

- Bayley-III scores with mean = 100, sd=15
- 19% deaths and severe disability each assigned a Bayley-III score of 40

Then

- overall expected mean is M0 = .19*40+.81*100 = 88.6
- Variance $19*(40\text{-mo})^2 + .81*(100\text{-mo})^2 + .81*15^2 = 736.29$; sd = (27.13^2)
- If intervention increases mean in survivors to 106, then overall expected mean=93.46, variance 852.64 sd (27.13^2)
- with n=700 per group, the expected difference in means =93.46 – 88.6 = 4.86 power; stand error = 1.51, SE assuming no effect = 1.45
- Power 91%, p0.05

Missing primary outcomes

The primary outcome is the Bayley-III Scores. These scores might be missing under certain circumstances:

1. If the infant dies before neurodevelopmental assessment, they were recorded as a score of 55 in the cognitive domain, 46 in the motor domain and 47 in the language domain (the minimum score for each scale).

2. If an infant failed to complete an assessment that has been started they were scored according to what they have done plus a fail recorded for all items following their refusal to carry on. A minimum score of 65 was set.

3. Infants who were unable to be assessed because of severe neurodevelopment disability were scored 55 in the cognitive domain, 46 in the motor domain and 47 in the language domain (the minimum score for each scale).

4. Neurodevelopment scores were imputed for infants who were untraceable or whose mothers refused to take part in an assessment, provided such refusal was not the result of disability – in which case point 3 applied. Following the Statistical Analysis Plan, the scores were imputed from gestational age, BAPM level and hypothyroxinaemic status recorded for other infants in the trial; however, we also added neurodevelopmental assessor, infant gender and randomisation centre. Multiple imputation was used.

5. Hypothyroxinemic status on day 14 was selected as the blood collection day to determine the imputation calculation as it had the strongest association with the Bayley-III scores.

SECTION 3, TRIAL PROCEDURES

1. No infant's allocation was unblinded during the trial; neither during the intervention phase, during the assessment phase, nor during analysis.
2. Protocol violations/deviations
   There were no protocol violations. There were three groups of protocol deviation
   - **Procedural errors** –these were primarily reported with errors concerning the daily trial solutions; there were very few other procedural errors (Supplementary Table 7)
   - **Infant exposures to additional iodide** – all infants exposed to additional iodide, such as via contrast media or topical iodide used for skin cleansing, were withdrawn from trial solutions and had thyroid function monitored (following a trial guidance sheet). During the intervention phase of the trial 79 infants were withdrawn from the trial solutions due to exposure to additional iodide. Of the exposed infants two were found to have transient thyroid dysfunction.
   - **Neurodevelopmental assessment** – for the I2S2 trial the Bayley-III should be completed at 2 years of age corrected for prematurity plus or minus one month. Of the 997 tests undertaken 112 (22%) were outwith this window for the iodide supplemented group and 115 (23%) for the placebo group (Supplementary Table 8). The Bayley-III scores are standardized for age and the inclusion of such infants does not invalidate the outcome.

SUPPLEMENTARY TABLE 7 Proportion of Infants Receiving Expected Number of Daily Trial Solutions

Daily trial solutions	Iodide		Placebo	
Total infants at intervention stage	**N=631**		**N=628**	
Number of infants who had a missed dose recorded	209	(33.1%)	188	(29.9%)
Number of infants receiving no solutions[A]	3	(0.5%)	4	(0.6%)
Number of infants who received the trial solution on correct day ±1 day[B]	545	(86.4%)	544	(86.6%)
Number of infants who received the trial solution on correct day ±2 days[B]	64	(10.1%)	67	(10.6%)
Number of infants who received the trial solution on correct day ± 3+ days[B]	19	(3.0%)	13	(2.2%)

[A] i.e. infants either died or withdrew before trial solutions were started
[B] ± days taking into account number of days on trial solution plus missed doses recorded; time of trial solutions final dose not recorded, incomplete daily logs with missing information

SUPPLEMENTARY TABLE 8 Number of Infants Completing the Bayley-III Assessment within and outwith the Recommended Time of 2 years corrected for prematurity ± 30 days

	Iodide		Placebo	
Total Infants completing Bayley III assessment	**N=498**		**N=499**	
Infants seen ± 30 days i.e. according to Bayley-III recommendation	386	(78%)	384	(77%)
Infants seen ± 37 days	28	(6%)	33	(7%)
Infants seen ± 2 months	32	(6%)	32	(6%)
Infants seen ± 3 months	26	(5%)	24	(5%)
Infants seen ± 4–6 months	19	(4%)	22	(4%)
Infants seen ± 7–16 months	7	(1%)	4	(1%)

SUPPLEMENTARY TABLE 9 Loss to Follow-up According to Stage of the Trial

		Iodide	Placebo
Total Infants Randomised	**N=1,275**		
Infants randomised in error	**2**		
Intervention stage	**N=1,273**	**N=637**	**N=636**
Consent withdrawn: No data used [A]		6	8
Consent withdrawn: Data used to point of withdrawal		2	4
Withdrawn from solutions Ongoing data collected and follow up undertaken:			
Exposure to iodide		(27)	(24)
Parental wish		(1)	(3)
Maternal iodide supplementation		-	(1)
Raised TSH on trial blood spot card		(5)	(2)
Raised TSH – jaundice screen		(1)	-
Maternal/fetal Graves' disease		(1)	-
Total		35	30
Deaths		61	59
Follow up Stage	**N=1,133**	**N=568**	**N=565**
Consent withdrawn: Data used to point of withdrawal		4	4
Deaths[B]		4	7
Severely disabled		9	11
Lost to follow up		53	44
2 year follow up Bayley-III assessment completed		498	499
Primary analysis (under intention-to-treat)	**N=1,259**	**N=631**	**N=628**

[A] Numbers **not** included for Primary analysis (under intention-to-treat)

[B] Causes of death unknown